Asymmetric Catalysis

DOI: 10.1002/anie.201108061

# Atropoisomeric (P,N) Ligands for the Highly Enantioselective Pd-Catalyzed Intramolecular Asymmetric α-Arylation of α-Branched Aldehydes**

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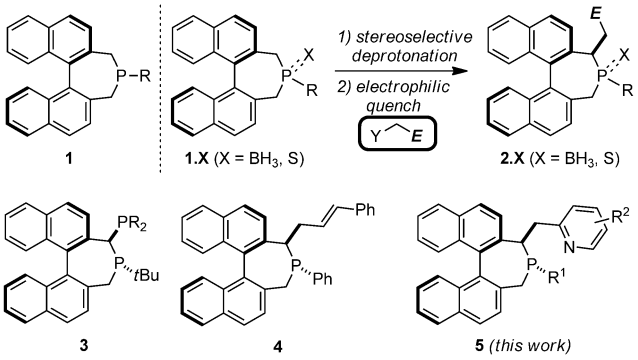
*Dedicated to Professor E. Peter Kündig on the occasion of his 65th birthday*

The prevalence of α-chiral aldehydes as pivotal intermediates in synthesis and the challenge posed by their stereocontrolled preparation have attracted increased interest from the synthetic organic community in the last decades.[1] Amongst successful examples of asymmetric catalytic reactions leading to α-chiral aldehydes, the metal-catalyzed hydroformylation of olefins[2,3] and a variety of aminocatalytic additions to aldehydes relying either on enamine or singly occupied molecular orbital (SOMO) activations have become the most dominant and inspiring strategies.[4–6] Interestingly, despite major advances in these areas, very few catalytic asymmetric approaches enable the preparation of α-chiral aldehydes possessing a quaternary stereogenic center with high efficiency and, more importantly, broad diversity.[7]

As part of our ongoing research program aimed at the stereoselective preparation of chiral aldehydes, we became interested in identifying strategies that would complement the catalytic asymmetric isomerization of allylic alcohols[8] and the catalytic asymmetric hydroboration of terminal olefins[9] developed in our laboratory. The Pd-catalyzed direct α–arylation of aldehydes pioneered by Muratake and co-workers appeared particularly attractive to us because of the ready access to quaternary stereogenic centers it offers.[10–13] As a testimony to the hurdles inherent in the development of asymmetric variants of C–C bond-forming reactions, to date there is only one example of a Pd-catalyzed enantioselective intramolecular asymmetric α–arylation of aldehydes. The observation made by Buchwald and co-workers [14] that heterotopic (P,N) ligands were superior to homotopic diphosphine ligands for this transformation [15] guided our ligand design. Therefore, we initiated efforts towards the development of a new family of $C_1$-symmetric chiral (P,N) ligands elaborated around the well-established binepine scaffold **1**.[16] Herein, we report the successful application of this new class of highly modular chiral ligands in the context of the Pd-catalyzed intramolecular asymmetric α-arylation of α-branched aldehydes.




The synthetically versatile binepine structure **1** has been almost exclusively used as a monodentate ligand in a variety of catalytic asymmetric transformations.[16] $C_1$-symmetric bidentate scaffolds derived from **1** are the bisphosphine ligand **3**[17] and the bidentate (P,η²-olefin) ligand **4**.[18] During the synthesis of ligands **3** and **4**, Zhang and Widhalm independently established that stereoselective monosubstitution of protected binepines (**1.X**→**2.X**) can be achieved by deprotonation of the most exposed pseudo-apical benzylic proton and a subsequent quench with appropriate electrophiles. Inspired by these precedents, we reasoned that the introduction of a 2-methylpyridyl unit would readily give access to **5**, a new type of $C_1$-symmetric chelating (P,N) ligand potentially offering a high level of structural variations through modular assembly of the P- and N-containing building blocks. As for **3**–**4**, these ligands would possess added complexity because of the newly formed stereogenic centers at the benzylic position and the phosphorus atom upon monosubstitution. To ensure facile purification, readily accessible borane-protected binepines **1**·$BH_3$ were prepared according to literature procedures (Scheme 1).[19] Subsequent deprotonation with *t*BuLi (2.5 equiv) at −78 °C in THF, followed by addition of a threefold excess of the appropriate 2-bromopyridyl derivative, furnished **6a**–**i** in moderate to

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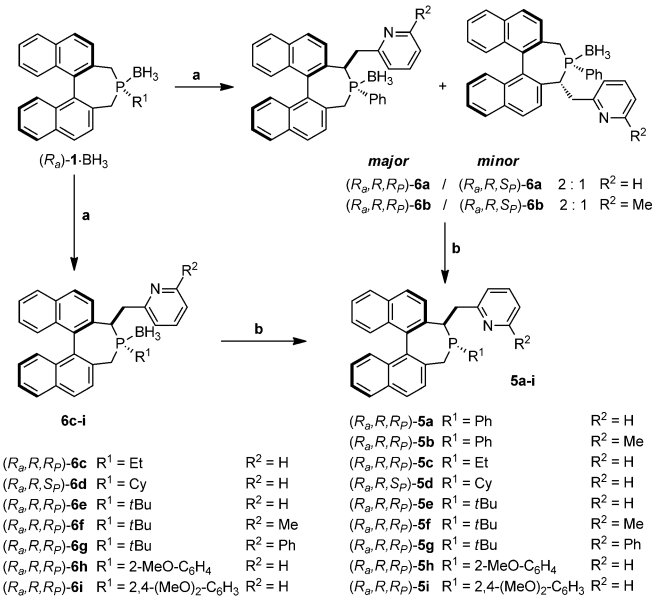
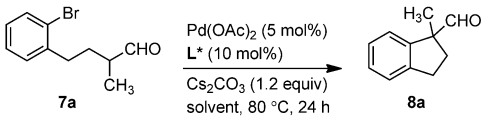
[**] This work was supported by the State Secretariat for Education and Research, the Swiss National Foundation (project no. 200020_132681). Roche is also acknowledged for support through an unrestricted grant. Prof. J. Lacour (University of Geneva) is warmly thanked for a generous gift of (*R*)- and (*S*)-binol. We thank one referee for constructive comments and suggestions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201108061.



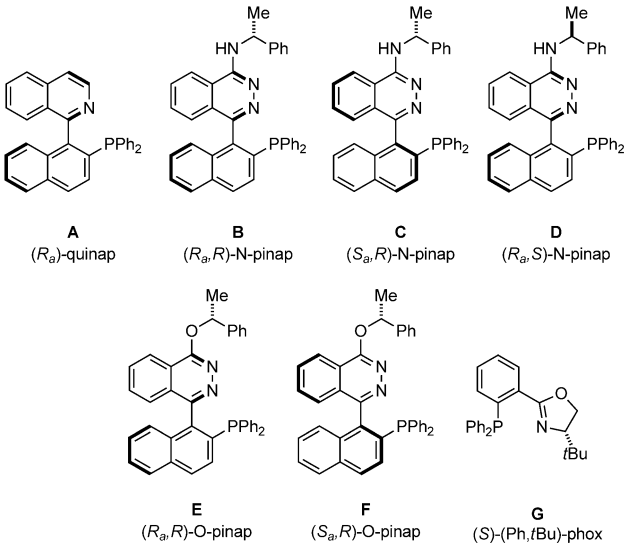

***Scheme 1.*** Synthesis of phosphino–pyridine ligands **5a–i**. Reagents and conditions: a) *t*BuLi, −78 °C to −40 °C; then 2-(bromomethyl)pyridine ($R^2$ = H), 2-(bromomethyl)-6-phenylpyridine ($R^2$ = Me), or 2-(bromomethyl)-6-methylpyridine ($R^2$ = Ph), −78 °C to RT, 24 h; b) $Et_2NH$, 80 °C, 4 days. Cy = cyclohexyl.

***Table 1:*** Reaction optimization.[a]




| Entry | Solvent | L* | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | toluene | ($R_a$,*R*,$R_P$)-**5e** | 25[d] | 66 (*S*) |
| 2 | toluene | ($R_a$,*R*,$R_P$)-**5e** | 60 | 66 (*S*) |
| 3 | toluene | ($R_a$,*R*,$R_P$)-**5e** | 29[e] | 59 (*S*) |
| 4 | toluene | ($R_a$,*R*,$R_P$)-**5a** | 17 | 86 (*S*) |
| 5 | toluene | ($R_a$,*R*,$R_P$)-**5b** | 23 | 59 (*S*) |
| 6 | toluene | ($R_a$,*R*,$R_P$)-**5c** | 10 | 84 (*S*) |
| 7 | toluene | ($R_a$,*R*,$S_P$)-**5d** | 9 | 70 (*S*) |
| 8 | toluene | ($R_a$,*R*,$R_P$)-**5f** | 57 | 22 (*S*) |
| 9 | toluene | ($R_a$,*R*,$R_P$)-**5g** | < 5 | n.d.[f] |
| 10 | toluene | ($R_a$,*R*,$R_P$)-**5h** | 12 | 96 (*S*) |
| 11 | toluene | ($R_a$,*R*,$R_P$)-**5i** | 35 | 96 (*S*) |
| 12 | DMF | ($R_a$,*R*,$R_P$)-**5i** | 60 | 96 (*S*) |
| 13 | DMF | ($R_a$,*R*,$R_P$)-**5i** | 75[g] | 96 (*S*) |
| 14 | DMF | ($R_a$,*R*,$R_P$)-**5i** | > 99[h] | 85 (*S*) |
| 15 | DMF | ($R_a$)-**A** | 65[g] | 37 (*S*) |
| 16 | DMF | ($R_a$,*R*)-**B** | 85[g] | 16 (*R*) |
| 17 | DMF | ($S_a$,*R*)-**C** | 90[g] | 27 (*S*) |
| 18 | DMF | ($R_a$,*S*)-**D** | 90[g] | 21 (*R*) |
| 19 | DMF | ($R_a$,*R*)-**E** | 95[g] | 12 (*R*) |
| 20 | DMF | ($S_a$,*R*)-**F** | 99[g] | 8 (*S*) |
| 21 | DMF | (*S*)-**G** | 5[g] | 51 (*S*) |

[a] Average of at least two independent experiments (0.25 mmol scale). Standard conditions: $Pd(OAc)_2$ (5 mol%), chiral ligand (10 mol%), cesium carbonate (1.2 equiv), 80 °C. [b] Determined by $^1$H NMR. [c] Determined by GC analysis using a chiral-phase column. Absolute configuration assigned by analogy with literature data. [d] 5 mol% of ligand were employed. [e] 2.2 Equivalents of base were employed. [f] n.d. = not determined. [g] Yield of isolated product after 48 h. [h] Reaction performed at 110 °C.




good yields after purification by column chromatography. Whereas **6a** and **6b** were obtained as a 2:1 mixture of two separable diastereoisomers (65% and 71% of combined yield, respectively), **6c–i** were systematically obtained as single diastereoisomers (39–82% yield). The relative stereochemistry of each ligand precursor was unambiguously established by 2D NMR analyses. We attribute the formation of the minor diastereoisomer ($R_a$,*R*,$S_P$)-**6a,b** to the relatively similar accessibility of both pseudo-apical benzylic protons in **1**·$BH_3$ ($R^1$ = Ph) owing to the small steric bias between the borane and the phenyl ring. This is particularly evident when compared to the results obtained with the sterically more demanding P substituents employed in this study. After deprotection by refluxing **6a–i** in an excess of diethylamine for few days and removal of the volatiles, ligands **5a–i** were isolated as off-white crystalline solids in good to excellent yields (70–85%). Unexpectedly, quantitative interconversion of ($R_a$,*R*,$S_P$)-**5a,b** into ($R_a$,*R*,$R_P$)-**5a,b** by a formal P inversion was observed during the deprotection event.[20] Subsequent syntheses of **5a,b** were conveniently carried out without prior separation of the diastereomeric mixtures **6a,b**.

The potential of these new atropoisomeric phosphino–pyridine ligands was evaluated in the challenging α–arylation of α-branched aldehydes using **7a** as a model substrate. Preliminary investigations consisted of delineating the optimal conditions by varying the most common reaction parameters using in situ generated catalysts with ligand **5e**. A representative selection of the results obtained is reported in Table 1. Cyclization product **8a** was isolated in modest yield, but with a promising 66% *ee* when the reaction was performed at 80 °C in toluene with $Pd(OAc)_2$ (5 mol%), chiral ligand (5 mol%), and cesium carbonate (1.2 equiv) as a base (entry 1). Adjusting the relative stoichiometry between the different components revealed that a twofold excess of the ligand with respect to the catalyst gave higher yields of **8a**, whereas the use of two equivalents of the base slightly eroded the enantioselectivity of the product (entries 2 and 3). Several $Pd^0$ and $Pd^{II}$ precursors were also evaluated because the

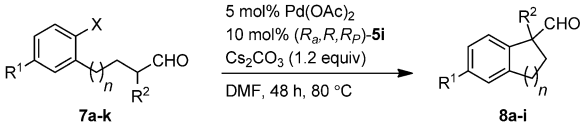
  

efficiency to generate the active species plays a key role on the rate of most cross-coupling reactions. Unfortunately, none of the other palladium sources surveyed offered a similar balance between activity and selectivity to that of our initial choice. Neither did other solvents and bases (See the Supporting Information). Under optimized conditions (see Table 1), variation of the ligand structure was next performed (entries 4–11). Replacement of the *tert*-butyl group at the phosphorus atom in ligand **5e** by a less-bulky and less-donating phenyl ring, such as in **5a**, led to a net increase in enantioselectivity while the yield of **8a** was substantially reduced (86% *ee*, 17% yield, entry 4). The use of an ethyl or a cyclohexyl substituent did not prove beneficial (entries 6 and 7). The presence of a methyl or a phenyl substituent at the 2-position of the pyridyl unit systematically affected the activity and, more importantly, the selectivity of the in situ generated catalyst (entries 5, 8, and 9). In an attempt to combine the best features of ligand **5a** (aromatic P substituent) and **5e** (electron-rich phosphine, sterically demanding substituent), ligands **5h** and **5I**, which both contain an *ortho*-methoxy substituent and, in the case of **5I**, an additional *para*-methoxy group, were designed.[21] To our delight, both of them delivered **8a** with unprecedented levels of enantioselection, albeit with moderate yields (96% *ee*, 12% yield and 96% *ee*, 35% yield, respectively; entries 10 and 11). Suspecting the solubility of the base may be crucial in obtaining a satisfactory reaction rate, DMF was finally evaluated as solvent for this cross-coupling reaction.[22] Gratifyingly, the yield of **8a** significantly improved under otherwise identical conditions (entry 12). When the reaction time was prolonged to 48 h, **8a** was obtained in 75% yield and 96% *ee* (entry 13). Reactions performed at higher temperatures led to improved rates, but at the expense of the enantioselectivity (entry 14).[23]

To further validate our initial ligand design, a comparative study was conducted using commercially available chiral (P,N) ligands **A**–**G** that have proven successful in a number of other catalytic asymmetric transformations (entries 15–21).[15,24] Although the cyclization product was generally obtained in good to excellent yields, none of these scaffolds gave **8a** with levels of enantioselectivity comparable to those obtained with **5i**. Interestingly, ligand **G**, which was identified by Buchwald and co-workers as one of the most promising candidates in their seminal contribution,[14] displayed both reduced activity and enantioselectivity under our optimized reaction conditions.

The scope and limitations of the intramolecular α–arylation of a variety of α-branched aldehydes was next investigated, employing the new optimal conditions (Table 2). As one may expect from the reactivity trend of aryl halides in C–C bond-forming reactions, the use of aryl chloride precursor **7b** gave much lower yield of product while maintaining a very high level of enantioselectivity (entry 2). More surprisingly, the corresponding aryl iodide **7c** led to significantly diminished yield of the bicyclic aldehyde (entry 3). Although further studies are required to elucidate the origin of this phenomenon, it suggests that iodide may inhibit the coupling reaction, as recently observed in related Pd-catalyzed C–N cross-coupling processes.[25] *Para* substitution of the aryl bromide moiety with electron-withdrawing or electron-donating substituents was well-tolerated; products **8b**–**e** were obtained in practical yields with good to excellent enantioselectivities (entries 4–7). Whereas an α-ethyl substituent, as in **7h**, delivered the product in good yield and high enantioselectivity (entry 8), the use of a secondary alkyl substituent ($R^2 = i$Pr) had a deleterious effect on both the activity and the selectivity (entry 9). A six-membered ring (entry 10) and a product with a phenyl substituent (entry 11) could be formed quantitatively, albeit with much lower *ee* values. Initial efforts to extend this method to an intermolecular process have met with limited success.[26]

***Table 2:*** Substrate scope.[a]



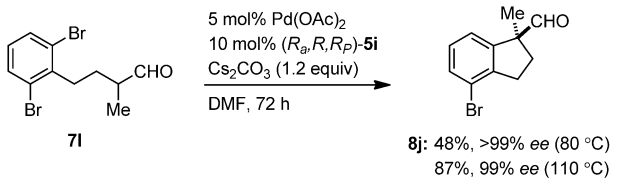

| Entry | 7 | X | *n* | $R^1$ | $R^2$ | 8 | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|---|
| 1 | **a** | Br | 1 | H | Me | **a** | 75 | 96 (*S*) |
| 2 | **b** | Cl | 1 | H | Me | **a** | 6[d] | 98 (*S*) |
| 3 | **c** | I | 1 | H | Me | **a** | 15 | 98 (*S*) |
| 4 | **d** | Br | 1 | F | Me | **b** | 66[e] | 95 (*S*) |
| 5 | **e** | Br | 1 | OMe | Me | **c** | 83 | 95 (*S*) |
| 6 | **f** | Br | 1 | $CF_3$ | Me | **d** | 91 | 92 (*S*) |
| 7 | **g** | Br | 1 | Me | Me | **e** | 52 | 87 (*S*) |
| 8 | **h** | Br | 1 | H | Et | **f** | 80 (>99)[f] | 94 (85)[f] (*S*) |
| 9 | **i** | Br | 1 | H | *i*Pr | **g** | 51 | 75 (*R*) |
| 10 | **j** | Br | 2 | H | Me | **h** | >99 | 20 (*S*) |
| 11 | **k** | Br | 1 | H | Ph | **i** | 99 | 35 (*R*) |

[a] Reactions performed on a 0.5 mmol scale. Standard conditions: $Pd(OAc)_2$ (5 mol%), ($R_a$,*R*,$R_p$)-**5i** (10 mol%), cesium carbonate (1.2 equiv), DMF solvent, 80°C, 48 h. [b] Yield of isolated product. [c] Determined by GC or HPLC analysis using a chiral-phase column. Absolute configuration assigned by analogy with literature data. [d] Along with 49% of **7b** and 45% of hydrogenolysis product. [e] Contains 34% of inseparable **7d**. [f] These values refer to the reaction carried out at 110°C.

Lautens and co–workers have recently demonstrated the ability of $t$Bu$_3$P to promote reversible oxidative addition into aryl bromide bonds at the catalytic level in the context of the palladium-catalyzed selective coupling of polyhalogenated substrates.[27,28] Remarkably, when dibrominated substrate **7l** was subjected to the optimized reaction conditions, the corresponding mono-brominated product **8j** was obtained in 48% yield and greater than 99% *ee* (Scheme 2). No traces of debrominated **7l** or **8j** were observed along with the remaining unreacted starting material (50% of recovered yield for **7l**). Upon increasing the reaction temperature to 110°C, **8j** could be obtained in 87% yield and 99% *ee*. This initial result suggests that ligand **5i**, like $t$Bu$_3$P, allows for reversible oxidative addition into aryl bromide bonds.

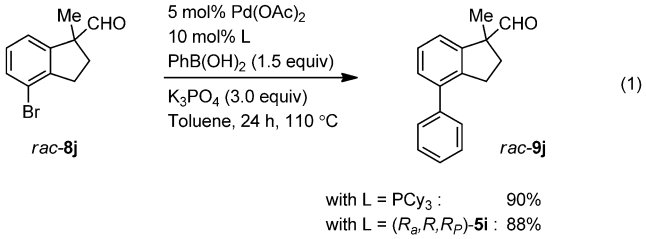
To further investigate whether the aryl bromide bond in **8j** is indeed reactive towards palladium catalysis, cyclization product *rac*-**8j** was prepared independently and subjected to a series of Suzuki cross-couplings using phenylboronic acid as a reaction partner. Under prototypical reaction conditions, using either $PCy_3$ or ligand **5i**, the corresponding product **9j**

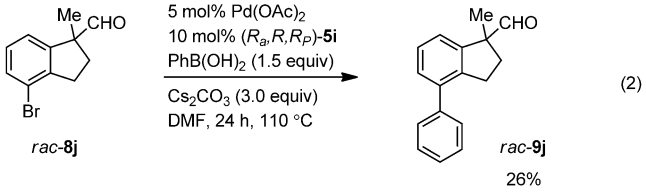



***Scheme 2.*** Selective intramolecular α-arylation of dibrominated substrate **7l** with ligand **5i**.

could be obtained in excellent yields in both cases [90% and 88% yield, respectively; Eq. (1)]. Furthermore, using ligand **5i** and reaction conditions that closely resemble those used for the α–arylation reaction (DMF, $Cs_2CO_3$, 110°C), the cross-coupling product was already isolated in 26% yield, after only 24 h [Eq. (2)].[29]




(1)




(2)

To gain preliminary information on the spatial arrangement of the new phosphino–pyridine ligands upon coordination to palladium, complex **10i** was synthesized in excellent yields by reacting a stoichiometric amount of ligand **5i** and $[(CH_3CN)_2PdCl_2]$ in dichloromethane for 2 h. Crystals of suitable quality for an X-ray diffraction analysis of **10i** were grown by layering a concentrated solution of dichloromethane with hexanes.[30] This complex displays a slightly distorted square-planar geometry around the palladium center (P–Pd–N = 93.25°) and the six-membered metallacycle adopts a boat-like conformation (Figure 1). The relative stereochemistry of the two newly formed stereogenic centers at the C and P atoms is in agreement with the initial NMR assignment. As expected, the stronger *trans* influence exerted by the P donor is evidenced by comparison of the Pd–Cl distances (Pd–Cl2 = 2.3803(8) Å vs. Pd–Cl1 = 2.2907(8) Å. No direct interaction between Pd and the oxygen of the *ortho*-methoxy substituent of the aryl ring on phosphorous is visible (Pd···O = 3.47 Å). Anion metathesis using two equivalents of AgOAc quantitatively converted **10i** into **11i**, a complex of general formula $[(\mathbf{5i})Pd(OAc)_2]$.

Next, complexes **10i** and **11i** were subjected to the optimized reaction conditions for the α-arylation of our

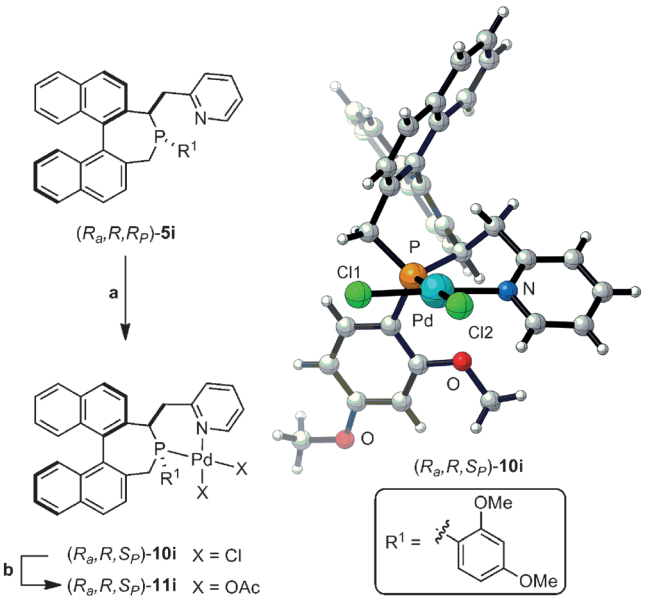
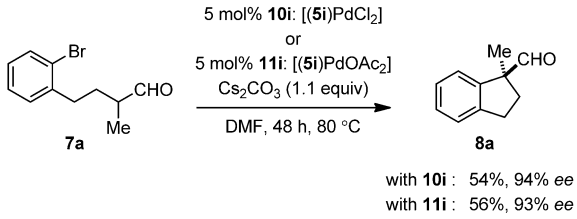



***Figure 1.*** Synthesis of two palladium complexes using $(R_a,R,R_P)$-**5i**, and CYL-view representation of $(R_a,R,S_P)$-**10i**. Reagents and conditions: a) $[Pd(CH_3CN)_2Cl_2]$, $CH_2Cl_2$, room temperature, 2 h (89% yield). b) AgOAc, $CH_2Cl_2$, room temperature, 1 h (99% yield). Relevant bond distances [Å] and angles [°]: P–Pd 2.2287(8), N–Pd 2.074(3), Pd–Cl2 2.3803(8), Pd–Cl1 2.2907(8); P-Pd-N 93.25(8).

model substrate **7a** using 5 mol% of catalyst (Scheme 3). Cyclization product **8a** was obtained in similar yields and enantioselectivities (54% yield, 94% *ee*; 56% yield, 93% *ee*,




***Scheme 3.*** Intramolecular α-arylation of a model susbtrate **7a** using well-defined complexes **10i** and **11i**.

respectively). It appears these well-defined palladium(II) complexes constitute a viable alternative to in situ generated catalysts, a method which requires the use of additional free ligand.[31] Of practical note, unlike the free (P,N) ligand, both **10i** and **11i** are air-stable materials, which simplifies the experimental setup of the catalytic reactions.

In conclusion, we have described the straightforward synthesis of a new class of highly modular chiral phosphino–pyridine ligands articulated around the atropoisomeric binepine scaffold. These ligands, which combine three elements of chirality, were found to be highly enantioselective in the notoriously challenging asymmetric α-arylation of aldehydes for a variety of α-branched substrates. Of particular note is the observation of a reversible oxidative addition of aryl bromides under catalytic conditions. This is, to the best of our knowledge, the first example of a chiral ligand exhibiting such

behavior and we believe it opens novel perspectives in the context of asymmetric catalysis. Extension of this method to an intermolecular variant, further mechanistic studies into the origin of the reactivity and selectivity of this arylation reaction, and application of these new chiral (P,N) ligands to other asymmetric transformations are the focus of ongoing investigations in our laboratory.

Received: November 16, 2011
Revised: January 25, 2012
Published online: March 2, 2012

**Keywords:** α-arylation · asymmetric catalysis · ligand design · oxidative addition · palladium

[1] a) D. Evans in *Asymmetric Synthesis*, *Vol. 1* (Eds.: J. D. Morrison), Academic Press, New York, **1984**; b) D. Seebach, R. Imwinkelried, T. Weber in *Modern Synthetic Methods* (Eds.: R. Scheffold), Springer, Berlin, **1986**.

[2] For recent reviews on asymmetric hydroformylation, see: a) K. Nozaki in *Comprehensive Asymmetric Catalysis*, *Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto) Springer, Berlin, **1999**, chap. 11; b) C. Claver, P. W. N. M. van Leuween in *Rhodium-catalyzed Hydroformylation* (Eds.: P. W. N. M. van Leuween, C. Claver), Kluwer Academic Publishers, Dodrecht, **2000**, chap. 5; c) A. Guai, C. Godard, S. Castillón, C. Claver, *Tetrahedron: Asymmetry* **2004**, *15*, 1135 – 1146; d) J. Klosin, C. R. Landis, *Acc. Chem. Res.* **2007**, *40*, 1251 – 1259.

[3] For recent examples of asymmetric hydroformylation, see: a) T. P. Clark, C. R. Landis, S. L. Freed, J. Klosin, K. A. Abboud, *J. Am. Chem. Soc.* **2005**, *127*, 5040 – 5042; b) J. Mazuela, M. Coll, O. Pàmies, M. Diéguez, *J. Org. Chem.* **2009**, *74*, 5440 – 5445; c) X. Zhang, B. Cao, S. Yu, X. Zhang, *Angew. Chem.* **2010**, *122*, 4141 – 4144; *Angew. Chem. Int. Ed.* **2010**, *49*, 4047 – 4050; d) A. D. Worthy, C. L. Joe, T. E. Lightburn, K. L. Tan, *J. Am. Chem. Soc.* **2010**, *132*, 14757 – 14759; e) A. L. Watkins, C. R. Landis, *J. Am. Chem. Soc.* **2010**, *132*, 10306 – 10317; f) R. I. McDonald, G. W. Wong, R. P. Neupane, S. S. Stahl, C. R. Landis, *J. Am. Chem. Soc.* **2010**, *132*, 14027 – 14029; g) A. L. Watkins, C. R. Landis, *Org. Lett.* **2011**, *13*, 164 – 167.

[4] For recent reviews on enamine and SOMO catalysis, see: a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471 – 5569; b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232 – 6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138 – 6171; c) D. W. C. MacMillan, *Nature* **2008**, *455*, 304 – 308; d) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178 – 2189; e) P. Melchiorre, *Angew. Chem.* **2009**, *121*, 1386 – 1389; *Angew. Chem. Int. Ed.* **2009**, *48*, 1360 – 1363.

[5] For selected leading examples, see: a) N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450 – 451; b) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514 – 6518; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366 – 6370; c) H. Xie, L. Zu, H. Li, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886 – 10894; d) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582 – 585; e) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649 – 7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539 – 7542; f) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77 – 80; g) R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8835 – 8838; *Angew. Chem. Int. Ed.* **2008**, *47*, 8707 – 8710; h) H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 13600 – 13603; i) J. S. Harvey, S. P. Simonovich, C. R. Jamison, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260 – 4263.

[6] Notable recent progress has been made in the proposal of alternative approaches; see, for example: a) S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336 – 11337; b) G. Jiang, B. List, *Angew. Chem.* **2011**, *123*, 9643 – 9646; *Angew. Chem. Int. Ed.* **2011**, *50*, 9471 – 9474; c) A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286 – 9288.

[7] a) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037 – 2066; b) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945 – 2963; c) *Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis* (Eds: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**; d) M. Bella, T. Gasperi, *Synlett* **2009**, 1583 – 1614.

[8] a) L. Mantilli, C. Mazet, *Tetrahedron Lett.* **2009**, *50*, 4141 – 4144; b) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem.* **2009**, *121*, 5245 – 5249; *Angew. Chem. Int. Ed.* **2009**, *48*, 5143 – 5147; c) L. Mantilli, C. Mazet, *Chem. Commun.* **2010**, *46*, 445 – 447; d) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem. Eur. J.* **2010**, *16*, 12736 – 12745; e) A. Quintard, A. Alexakis, C. Mazet, *Angew. Chem.* **2011**, *123*, 2402 – 2406; *Angew. Chem. Int. Ed.* **2011**, *50*, 2354 – 2358.

[9] C. Mazet, D. Gérard, *Chem. Commun.* **2011**, *47*, 341 – 344.

[10] a) H. Muratake, H. Nakai, *Tetrahedron Lett.* **1999**, *40*, 2355 – 2358; b) H. Muratake, M. Natsume, *Tetrahedron Lett.* **2002**, *43*, 2913 – 2917.

[11] For recent reviews on the α-arylation of carbonyl compounds, see: a) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234 – 245; b) A. C. B. Burtoloso, *Synlett* **2009**, 320 – 327; c) C. C. C. Johansson, T. J. Colacot, *Angew. Chem.* **2010**, *122*, 686 – 718; *Angew. Chem. Int. Ed.* **2010**, *49*, 676 – 707; d) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082 – 1146.

[12] For leading references, see: a) Y. Terao, Y. Fukuoka, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2002**, *43*, 101 – 104; b) G. D. Vo, J. F. Hartwig, *Angew. Chem.* **2008**, *120*, 2157 – 2160; *Angew. Chem. Int. Ed.* **2008**, *47*, 2127 – 2130; c) R. Martín, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 7374 – 7377; *Angew. Chem. Int. Ed.* **2007**, *46*, 7236 – 7239; d) R. Martín, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 4561 – 4564.

[13] In Pd- and Ni-catalyzed asymmetric α-arylations of carbonyls, depending upon the nature of the starting material, the challenge is equally difficult. In the case of linear carbonyls, one faces the issue of obtaining enantioenriched arylated products without post-reaction epimerization from the base used in such C–C bond forming processes. In the case of α-branched carbonyls, the generation of quaternary stereocenters with a high degree of enantioinduction can be viewed as an equally demanding task; see Ref. [11] for further discussion. For very recent examples of highly enantioselective Pd-catalyzed α-arylations of ester enolates leading to tertiary stereocenters under mildly basic conditions, see: a) Z. Huang, Z. Liu, J. Zhou, *J. Am. Chem. Soc.* **2011**, *133*, 15882 – 15885; b) K. Kobayashi, Y. Yamamoto, N. Miyaura, *Organometallics* **2011**, *30*, 6323 – 6327.

[14] J. García-Fortanet, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 8228 – 8231; *Angew. Chem. Int. Ed.* **2008**, *47*, 8108 – 8111.

[15] P. J. Guiry, C. P. Saunders, *Adv. Synth. Catal.* **2004**, *346*, 497 – 537.

[16] For a review on binepines and their use as ligands or catalysts, see: S. Gladiali, E. Alberico, K. Junge, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 3744 – 3763.

[17] Q. Dai, W. Li, X. Zhang, *Tetrahedron* **2008**, *64*, 6943 – 6948.

[18] a) P. Kasák, K. Mereiter, M. Wildhalm, *Tetrahedron: Asymmetry* **2005**, *16*, 3416 – 3426; b) P. Kasák, V. B. Arion, M. Widhalm, *Tetrahedron: Asymmetry* **2006**, *17*, 3084 – 3090.

[19] a) K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oeheme, A. Monsees, T. Riermeier, M. Beller, *Tetrahedron: Asymmetry* **2004**, *15*, 2621 – 2631; b) S. Enthaler, G. Erre, K. Junge, J. Holz, A. Bomer, E. Alberico, I. Nieddu, S. Gladiali, M. Beller, *Org. Process Res. Dev.* **2007**, *11*, 568 – 577.

[20] The thermodynamic and kinetic aspects of this interconversion process are currently being studied in our laboratory and will be

reported in due course. For related systems, see: a) M. T. Reetz, J.-A. Ma, R. Goddard, *Angew. Chem.* **2005**, *117*, 416 – 419; *Angew. Chem. Int. Ed.* **2005**, *44*, 412 – 415; b) G. Keglevich, P. Bagi, A. Szöllösy, T. Körtvélyesi, P. Pongrácz, L. Kollár, L. Drahos, *J. Organomet. Chem.* **2011**, *696*, 3557 – 3563; c) C. H. Schuster, B. Li, J. P. Morken, *Angew. Chem.* **2011**, *123*, 8052 – 8055; *Angew. Chem. Int. Ed.* **2011**, *50*, 7906 – 7909; d) M. Stollenz, M. Barbasiewicz, A. J. Nawara-Hultzsch, T. Fiedler, R. M. Laddusaw, N. Bhuvanesh, J. A. Gladysz, *Angew. Chem.* **2011**, *123*, 6777 – 6781; *Angew. Chem. Int. Ed.* **2011**, *50*, 6647 – 6651.

[21] Attempts to prepare a ligand with a 2,4,6-trimethoxyphenyl substituent at the phosphorus have not been successful to date.

[22] The solubility of $Cs_2CO_3$ in DMF is .1195 g $mL^{-1}$; see: J. A. Cella, S. W. Bacon, *J. Org. Chem.* **1984**, *49*, 1122 – 1125.

[23] We found that all substrates had to be freshly oxidized prior to catalysis to ensure reproducible results. For similar reasons, the substrates were prepared by using DMP oxidation rather than Swern oxidation. Attempts to use microwave irradiation as an alternative to conventional heating led to inconsistent results. Both starting materials and products tend to decompose over prolonged periods of time even when kept under a nitrogen atmosphere at low temperature.

[24] For selected leading references on ligands **A**–**G**, see: a) J. M. Brown, D. I. Hulmes, T. P. Layzell, *J. Chem. Soc. Chem. Commun.* **1993**, 1673 – 1674; b) H. Doucet, E. Fernandez, T. P. Layzell, J. M. Brown, *Chem. Eur. J.* **1999**, *5*, 1320 – 1330; c) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 6097 – 6099; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971 – 5973; d) T. F. Knöpfel, P. Zarotti, T. Ichikawa, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 9682 – 9683; e) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 2651 – 2654; *Angew. Chem. Int. Ed.* **2002**, *41*, 2535 – 2538; f) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336 – 345; g) J. A. Enquist, Jr., B. M. Stoltz, *Nature* **2008**, *453*, 1228 – 1231.

[25] B. P. Fors, N. R. Davis, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 5766 – 5768.

[26] See the Supporting Information for details.

[27] S. G. Newman, M. Lautens, *J. Am. Chem. Soc.* **2010**, *132*, 11416 – 11417.

[28] For an initial observation in stoichiometric reactions, see: a) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 1232 – 1233; b) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 13944 – 13945.

[29] At this stage, we do not have evidence that a kinetic resolution takes place.

[30] CCDC 854033 (**10i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[31] The role of the second equivalent of ligand in the in situ experiments is not clear at this stage of our investigations. Addition of free ligand when using **10i** or **11i** does not improve the yield of the reaction, ruling out the possibility of the extra free phosphine acting as a reductant. In their seminal contribution, Buchwald and co-workers used a threefold excess of ligand with respect to palladium to attain high conversions; see Ref. [14].